

*Original Article*

## Cost-effectiveness of irbesartan in diabetic nephropathy: a systematic review of published studies

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### Abstract

**Background.** To review published studies on the cost-effectiveness of the use of irbesartan for treatment of advance overt nephropathy in patients with type 2 diabetes and hypertension.

**Methods.** Articles were identified based on a search of the PubMed databases using the keywords 'irbesartan', 'ESRD', 'cost-effectiveness', 'nephropathy' and 'costs', and by personal communication with the authors. Only studies published in the last 10 years were included. All costs data from the cost-effectiveness studies were inflated to 2003 Euros using published governmental conversion tables.

**Results.** Seven published studies were identified, spanning the following country settings: the US, Belgium and France, Germany, Hungary, Italy, Spain, and the UK. In each, the same pharmacoeconomic model was adapted using country-specific data to project and evaluate the clinical and cost outcomes of the treatment arms of the Irbesartan in Diabetic Nephropathy Trial (IDNT) (irbesartan, amlodipine or standard blood pressure control). Mean time to onset of ESRD was 8.23 years for irbesartan, 6.82 years for amlodipine and 6.88 years for the control (values were the same for Belgium, France, Germany, Hungary, Italy and Spain as transition probabilities for progression to ESRD were all derived from the IDNT). Mean cumulative incidence of ESRD was 36% with irbesartan, 49% with amlodipine and 45% with control treatment. Treatment with irbesartan was projected to improve life expectancy compared to both amlodipine and control in all seven published studies. Analysis of total lifetime costs showed that irbesartan treatment was cost saving compared to the other two treatment regimens, due to the associated

reduction in ESRD cases. Cost savings with irbesartan became evident very early; after 2–3 years of treatment in most settings.

**Conclusions.** Modelling studies based on the IDNT published to date suggest that irbesartan treatment in patients with type 2 diabetes, hypertension and advanced nephropathy is both life- and cost-saving compared to amlodipine or control.

**Keywords:** costs; cost-effectiveness; diabetes; end-stage renal disease nephropathy; hypertension; irbesartan; modelling

### Introduction

Renal impairment is a serious complication of type 2 diabetes mellitus and becomes life threatening if it progresses to end-stage renal disease (ESRD). The huge impact that ESRD has on health and health-care system budgets is of major concern to healthcare decision makers. In the Western world, type 2 diabetes is recognized as the major underlying cause of ESRD [1], and the incidence of both diabetes and diabetic renal disease has reached epidemic proportions [2].

ESRD is associated with a substantial clinical and economic burden that impacts significantly on health-care systems. Throughout the US and Europe the prevalence of ESRD is increasing. Any measures that limit its severity and likelihood of leading to death need to be considered when making decisions on how best to treat patients with this serious condition. In the US, more than 300 000 people had ESRD in 1998, resulting in total medical expenditures of USD 18 billion [3]. The ESRD population increases by ~6% per year and for the year 2010 Medicare ESRD expenditures are projected to be USD 28 billion [3]. In the UK, diabetic nephropathy is the single most common cause of ESRD with 24% of new ESRD patients

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having diabetes as a co-morbidity [4]. Overall, new cases of ESRD due to diabetes, renovascular disease and hypertension almost doubled between 1990 and 1999 [5]. Between 1993 and 1999 there was an annual increase of 5% in the prevalence of ESRD in France, where the median survival time of patients receiving renal replacement therapy is ~2.7 years [6–8]. Evidence from Spain supports these figures, with recent evidence indicating that type 2 diabetes is associated with substantial increases in the incidence of nephropathy and is the major underlying cause of ESRD, which has a 5-year survival rate of only 54% [9,10]. By optimally treating patients with type 2 diabetes, renal disease and hypertension it may be possible to avoid the substantial human and economic burden of the renal failure associated with patients in this condition.

Until recently, renoprotection with angiotensin receptor blockers had not been reported in patients with type 2 diabetic nephropathy. This changed in 2001 when Lewis *et al.* [11] published the findings of the Irbesartan in Diabetic Nephropathy Trial (IDNT). The IDNT was a multi-centre, double-blind, placebo-controlled study in which 1715 hypertensive patients with type 2 diabetes and advanced overt nephropathy (protein excretion >900 mg per 24 h) were randomized to treatment with either irbesartan (angiotensin 2 receptor antagonist), amlodipine (a dihydropyridine calcium channel blocker) or standard blood pressure control. Patients were tracked for a mean duration of 2.6 years. To achieve a target blood pressure of <135/85 mmHg throughout the trial, patients in all three treatment arms received additional standard antihypertensive medications included in the control arm if required [diuretics, beta blockers, alpha/beta blockers, peripheral vasodilators, peripheral adrenergic blockers, and central adrenergic blockers, but excluding angiotensin converting enzyme (ACE) inhibitors, other angiotensin-2-receptor antagonists and dihydropyridine calcium channel blockers]. The IDNT showed that treatment with irbesartan in patients with type 2 diabetes, proteinuria and hypertension resulted in an ~23% reduction in the risk of achieving the combined primary endpoint of doubling of serum creatinine (DSC, a strong predictor of progression to end-stage renal disease), onset of ESRD, or all-cause mortality, when compared with amlodipine (a dihydropyridine calcium channel blocker), and a 20% risk reduction when compared with the control. The differences between the treatment groups in this primary endpoint could not be fully explained by differences in blood pressure control between therapies, indicating an additional blood pressure-independent renoprotective effect associated with irbesartan [11].

The aim of this review is to identify and compare published studies which projected the cost-effectiveness and economic impact of irbesartan compared to amlodipine or control for patients with type 2 diabetes, overt nephropathy and hypertension derived from the IDNT.

## Literature search and data presentation

Articles for inclusion in this review were identified based on a search of the PubMed database using the keywords 'irbesartan', 'ESRD', 'cost-effectiveness', 'nephropathy' and 'costs', (singly and in various combinations) and by personal communication with the authors of search hits. Only studies published in the last 10 years were included in the review. Seven published studies were identified, spanning the following country settings: the US [12], Belgium and France [13], Germany [14], Hungary [15], Italy [16], Spain [17], and the UK [18]. In each study a pharmacoeconomic model was used to project and evaluate the clinical and cost outcomes of the treatment arms of the IDNT. The same model was used in all the country settings, but was adapted to each setting by integrating country-specific data. For the purposes of comparison, all costs data were inflated to 2003 Euros using conversion tables from governmental websites in France (<http://www.insee.fr/en/indicateur/achatfranc.htm>), Germany (<http://www.destatis.de/indicators/e/vpi001aj.htm>), the US (<http://stats.bls.gov/cpi/>) and the UK (<http://www.statistics.gov.uk/pdfdir/cpi1104.pdf>). The latter was also used to inflate costs from Belgium, Hungary and Spain. To convert UK, US and Hungarian costs to Euros, the following exchange rates were applied: €1 = GBP 0.70232; USD 1.30137; HUF 245.660.

## Modelling approach

In each of the seven published cost-effectiveness analyses, a Markov model developed using DATA Pro decision analysis and simulation software (TreeAge Software Inc., Williamstown, MA) was used to simulate the progression of a hypothetical cohort of patients with type 2 diabetes, advanced overt nephropathy and hypertension to DSC, ESRD and death in a variety of country settings. Markov models are a standard method for simulating the course of progressive, long-term diseases, and have been used extensively in chronic diseases like diabetes [19–21]. The model used is described in some detail elsewhere [12,13], but a brief overview has been provided for the purposes of this review.

The characteristics of the cohort at the start of the simulation were equivalent to those reported in IDNT [11]. The model was structured such that patients could progress through states from advanced overt nephropathy to DSC, ESRD, and death based on treatment-specific transition probabilities taken from the IDNT as previously described by Rodby *et al.* [12]. The treatment choices simulated in the model were based on those studied in the IDNT: irbesartan (75–300 mg per day), amlodipine (2.5–10 mg per day), or standard blood pressure control (control arm) to achieve a target blood pressure of <135/85 mmHg. Country-specific transition probabilities for the ESRD states (ESRD, dialysis, transplantation) were utilized in the Belgian,

**Table 1.** Summary of projected improvements in life expectancy

Country	Lifetime							
	25-year timeframe				10-year timeframe			
	Undiscounted LE		Discounted LE		Undiscounted LE		Discounted LE	
	Irbesartan vs amlodipine	Irbesartan vs control	Irbesartan vs amlodipine	Irbesartan vs control	Irbesartan vs amlodipine	Irbesartan vs control	Irbesartan vs amlodipine	Irbesartan vs control
Belgium [13]	0.71	0.91	0.46	0.62	0.13	0.26	0.10	0.22
France [13]	0.69	0.90	0.45	0.61	–	–	–	–
Germany [14]	–	–	–	–	–	–	–	–
Hungary [15]	0.29	0.63	0.15	0.36	0.07	0.23	0.05	0.16
Italy [16]	0.59	0.84	0.30	0.46	0.15	0.31	0.10	0.22
Spain [17]	0.46	0.75	0.21	0.37	0.1	0.25	0.06	0.17
UK [18]	0.38	0.70	0.31	0.58	0.08	0.23	0.07	0.21
US [12]	–	–	0.65	0.76	–	–	0.19	0.30

LE, life expectancy.

French, German, Hungarian, Spanish, UK and US settings. Mortality rates from the IDNT were assumed to remain constant for the first 10 years of the simulation in all studies, and then country-specific mortality data were used thereafter.

Country-specific cost inputs were used for drug treatments (including study drugs and adjuvant medications as required), renal dialysis and renal transplantation, and discounting of costs and clinical benefits was applied according to country-specific guidelines. The clinical benefits in the Belgian, French, and US settings were discounted at a rate of 3% per annum. In Hungary and Italy an annual discount rate of 5% was applied. The Spanish study utilized a discount rate of 6% per annum, and a discount rate of 1.5% per year was applied to clinical benefits in the UK setting. Costs in the Belgian, French and US settings were discounted at a rate of 3% per annum. In Germany, Hungary and Italy an annual rate of 5% was applied to costs, and in the Spanish and the UK settings a rate of 6% was used.

The acquisition costs of medications, management costs and treatment of ESRD were assumed to remain constant over the course of each simulation. A third party payer perspective was taken for all the costs used in each of the studies reviewed. Since the model was designed to assess incremental costs only, costs that were similar between the treatment arms (e.g. visits to the general practitioner, cardiovascular events, urinary albumin monitoring and other investigations) were excluded from the analyses.

## Development of ESRD

Data for ESRD projections have been published for Belgium, France, Germany, Hungary, Italy and Spain, but not for the UK or the US. Because the transition probabilities from the states progressing to ESRD were taken from the IDNT rather than country-specific data, the model produced the same projections for all six

countries. Over a 10-year timeframe the mean time to onset of ESRD was 8.23 years for irbesartan, 6.82 years for amlodipine and 6.88 years for the control. This represents differences of 1.41 years between irbesartan and amlodipine, and 1.35 years between irbesartan and the control. The mean cumulative incidence of ESRD over the 10-year timeframe was 36% for irbesartan, 49% for amlodipine and 45% for the control. Since the UK and the US were simulated using the same model and transition probabilities, it could be expected that the results would be the same for these countries (although these data were not published).

## Impact on life expectancy

Life expectancy was improved in the irbesartan group compared to the amlodipine and control groups in all the countries reviewed, with the exception of Germany where values were not reported. In the UK study, life expectancy projections were reported only in relative terms, comparing irbesartan to amlodipine and control (Table 1). In the US study, such projections were only reported in terms of discounted life years. More life expectancy data were available, however, for comparison between the studies performed in the other five country settings. A consistent pattern was recognizable in life expectancy projections over a 25-year timeframe (Table 2). Treatment with irbesartan was projected to extend life further than that with either amlodipine or control. This pattern was observed in all seven country settings with published data (Table 1). Whilst only discounted life expectancy was reported in the US study, the values follow the same pattern: the projected life expectancy was 7.99 years for irbesartan, 7.34 years for amlodipine and 7.23 years for control.

Table 1 shows the projected improvements in life expectancy following treatment with irbesartan compared to both amlodipine and control. Both undiscounted and discounted life years were recorded and timeframes of 10 and 25 years were available

**Table 2.** Summary of life expectancy projections (25-year timeframe)

Country/discount rate	Mean undiscounted life expectancy (years)			Mean discounted life expectancy (years)		
	Irbesartan	Amlodipine	Control	Irbesartan	Amlodipine	Control
Belgium/3% [13]	10.59	9.88	9.68	8.57	8.11	7.95
France/3% [13]	10.61	9.92	9.71	8.58	8.13	7.97
Germany/NR [14]	–	–	–	–	–	–
Hungary/5% [15]	11.60	11.32	10.98	8.03	7.87	7.67
Italy/5% [16]	10.79	10.20	9.95	7.63	7.63	7.17
Spain/6% [17]	11.08	10.62	10.33	7.32	7.11	6.95
UK/1.5% [18]	–	–	–	–	–	–
US/3% [12]	–	–	–	7.99	7.34	7.23

NR, not reported.

**Table 3.** Summary of total mean lifetime cost per patient (25 years)

Country/discount rate	Mean total lifetime cost per patient (€)			Mean cost of ESRD per patient (€) (percentage of mean total lifetime cost)		
	Irbesartan	Amlodipine	Control	Irbesartan	Amlodipine	Control
Belgium/3% [13]	79 080	100 878	91 321	74 722 (94%)	97 708 (97%)	90 067 (99%)
France/3% [13]	95 198	122 809	111 886	92 081 (97%)	120 113 (98%)	110 782 (99%)
Germany/5% <sup>a</sup> [14]	45 430	60 356	54 454	–	–	–
Hungary/5% [15]	41 488	51 646	46 824	36 950 (89%)	48 878 (95%)	45 025 (96%)
Italy/5% <sup>a</sup> [16]	41 692	55 222	49 825	37 257 (89%)	51 531 (93%)	47 514 (95%)
Spain/6% [17]	51 969	66 052	59 830	47 512 (91%)	62 768 (95%)	57 841 (97%)
UK/6% <sup>a</sup> [18]	30 627	40 208	36 138	26 094 (85%)	36 633 (91%)	33 969 (94%)
US/3% [12]	91 672	113 257	104 482	–	–	–

<sup>a</sup>10 year data available only.

for comparison (no data were available in the German setting). In Belgium irbesartan treatment, when compared to amlodipine, was projected to extend life by 0.71 undiscounted life years (0.46 discounted), and by 0.91 undiscounted life years (0.62 discounted) when compared to control over a 25-year timeframe. A similar pattern is seen in the other country settings with the exception of Germany. Undiscounted life expectancy data were not available from the US study, and no 10-year timeframe data were available for France, but it has been described as being comparable to that in the Belgian setting [13].

### Summary of costs and cost-effectiveness

A summary of the total mean lifetime costs per patient are recorded in Table 3 along with the mean costs of ESRD per patient. A 25-year timeframe was available for comparison between Belgium, France, Hungary, Spain and the US. A 10-year timeframe was used in the German, Italian and UK studies. The total mean lifetime costs per patient ranged from €41 488; €51 456 in Hungary for irbesartan, amlodipine and the control, respectively, to €95 198; €122 809 and €111 886, respectively, in France. These costs in all eight country settings were less for irbesartan when compared to amlodipine and the control. ESRD costs

accounted for the majority of total lifetime costs in all treatment arms (89–99%) where values were reported. Unfortunately, no data were available regarding the cost of ESRD in the German and the US setting.

A substantial proportion of the cost savings were realized in the 10-year, base-case timeframe (Table 4). Over this period irbesartan was associated with cost savings of €15 397 and €9 526 per patient in Belgium, and €20 550 and €13 617 in France, *vs* amlodipine and control, respectively. These results were consistent with published results for Germany, Hungary, Italy, Spain, the UK and the US. Eighty percent of overall savings were achieved within 9–11 years of treatment in Belgium, France and Spain.

Irbesartan, in fact, resulted in cost savings very early, usually within 2–3 years of treatment. This was the case in the Belgian, French, Italian, Spanish, UK and US settings. In the Belgian setting, after only 5 years, costs savings were €5335 and €3163 *vs* amlodipine and the control, respectively. In the French setting these savings were €7715 and €5164 *vs* amlodipine and the control, respectively. Cost savings in the UK setting due to avoided or delayed ESRD were evident after 3 years compared to the amlodipine group, and after 4 years compared to the control group. In the US setting, the model predicted that irbesartan would save €3462 and €2280 compared with amlodipine and the control, respectively, after 3 years.



**Table 4.** Summary of projected cost savings (€)

Country	Lifetime			
	25-year timeframe		10-year timeframe	
	Irbesartan vs amlodipine	Irbesartan vs control	Irbesartan vs amlodipine	Irbesartan vs control
Belgium [13]	21 798	12 241	15 397	9526
France [13]	27 611	16 688	20 550	13 617
Germany [14]	–	–	15 445	9338
Hungary [15]	10 158	5336	5675	3046
Italy [16]	17 003	9418	13 530	8133
Spain [17]	14 083	7861	10 261	6175
UK [18]	13 457	7300	7515	4280
US [12]	21 585	12 810	19 555	13 158

## Sensitivity analyses

The sensitivity analyses in all countries determined that the parameter with the greatest single impact on life expectancy was the annual probability of death in patients with overt nephropathy but no progression to DSC and ESRD (taken from the IDNT), closely followed by the annual probability of death in patients with ESRD receiving dialysis (taken from country-specific published sources). Any treatment which reduces the incidence of ESRD would be expected, therefore, to prolong life significantly. In the Spanish study, it was determined that irbesartan would remain life saving compared to amlodipine with up to a 10% increase in the probability of dying in patients with overt nephropathy but no progression to DSC and ESRD in the irbesartan treatment arm. This probability could be increased by as much as 18% with irbesartan remaining life saving compared to the control treatment.

Since the parameter with the greatest single impact on total lifetime costs was the annual cost of dialysis, one would expect that treatments which lowered the likelihood of dialysis being required would be expected to lower costs. By significantly reducing the incidence of ESRD, irbesartan treatment both extended life and reduced total costs in all of the countries reviewed.

## Discussion and conclusions

Type 2 diabetes patients with overt nephropathy and hypertension are at a very high risk of developing ESRD. It was hypothesized that, based on the results of the IDNT where irbesartan significantly reduced the progression from overt nephropathy to DSC and ESRD, treatment with irbesartan may have a substantial impact on the clinical outcomes and costs in this patient group. This review identified a number of studies where various country-specific clinical and costs data were processed through one published and peer-reviewed pharmacoeconomic Markov model. Where

life expectancy was analysed, improvements in life expectancy were forecast with irbesartan treatment vs amlodipine and vs the control after 10 years. The anticipated gains in life expectancy, due to delay in the onset of ESRD, compare very well with other established interventions in healthcare [22,23]. A reduction in overall costs per patient was observed with irbesartan treatment compared to amlodipine or control in all eight countries reviewed. In Belgium, France, Italy, Spain, the UK and the US cost savings were evident after 3 years.

The sensitivity analyses performed in the modelling studies demonstrated that these findings were robust under variation in a range of assumptions. Key factors were the probabilities of mortality in patients with either overt nephropathy before progression to more serious disease (derived from IDNT data), and in those with ESRD (derived from country-specific data). The key costs driver was the costs associated with dialysis.

Pharmacoeconomic modelling is commonly used in health economics, but it has some limitations that should be considered to place these findings properly into context. In order to translate changes in intermediate clinical outcomes to long-term costs, projections are made beyond known clinical trial periods, which requires assumptions to be made on the long-term effects of treatment in a given patient population. For example, patients in the IDNT were followed for a mean duration of 2.6 years. A longer-term study may have produced results that were more meaningful for cost-effectiveness projections with long timeframes. It could also be argued that modelling studies based on clinical trials do not accurately reflect the real-life situation, as they fail to take into account issues such as compliance, patient and physician preference, etc. Moreover, since costs are based on current figures, they may not truly reflect future costs despite the application of discounting. However, in the absence of large-scale, long-term epidemiological study data, modelling is a valuable technique by which long-term predictions can be made to assist healthcare decision-makers determine how best to allocate scarce health resources.

Another potential limitation of this study is that our literature search identified seven publications based on the same Markov model, adapted using country-specific data to project and evaluate the clinical benefits and costs of irbesartan *vs* amlodipine and a control. It would have been interesting to have included data on the same interventions from a different model perspective of nephropathy to extend the comparison of findings further.

A number of key assumptions were made in the published modelling analyses that may have had an impact on their findings. For example, in all three treatment arms in the model, it was assumed that the transition probabilities returned to those of the control group after the 3-year trial period. In other words, only the trial effects of irbesartan and amlodipine were considered. This may have biased the analyses against irbesartan, as its renoprotective effects could well have been sustained beyond the trial period. However, this conservative assumption was made as it remains uncertain whether the observed effect of irbesartan would be sustained over a 10-year or 25-year period. It was also assumed that the mortality rates from the IDNT would remain constant for the first 10 years of the simulation [11]. This could also be biased against irbesartan, but the long-term influence which treatment with irbesartan has on delaying the onset of ESRD is not known. Another significant assumption made was that the acquisition costs of medications would remain constant over the 10-year simulation period. The possibility, therefore, of medications becoming cheaper in the future due to loss of patent protection was not taken into account. This may have overestimated the costs of irbesartan in the future, and may have therefore underestimated any cost savings that could be expected. It was assumed, conservatively, that in the absence of published comparisons of the effects of irbesartan, amlodipine and a standard control of hypertension in patients with ESRD, the probabilities of death or changing between dialysis and renal transplant states were not dependent on treatment arm if ESRD developed in a patient during the simulation. Therefore, it was not possible to analyse the influence that the various treatment arms may have had on the course of ESRD.

One of the shortcomings of the IDNT, and therefore in the modelling analyses based upon it, is that it did not include angiotensin-converting enzyme inhibitors, beta-blockers or other angiotensin 2 receptor blockers as treatments for type 2 diabetes patients with nephropathy and hypertension. Where type 1 diabetes and non-diabetic renal impairment have been modeled, it has been suggested that angiotensin-converting enzyme inhibitors may produce long-term cost savings [24–28]. A recent head-to-head trial compared the renoprotective effects of the ACE-inhibitor enalapril 20 mg daily *vs* the angiotensin II-receptor blocker telmisartan 80 mg daily in patients with type 2 diabetes and nephropathy [29]. Study endpoints included the change in glomerular filtration rate over 5 years, rates of ESRD and cardiovascular events; and rate of death

from all causes. Telmisartan was found to be non-inferior to enalapril as a renoprotective agent in this patient group, but no conclusions could be drawn as to whether or not this applied to patients with more advanced nephropathy. Further trials comparing irbesartan with ACE-inhibitors are required in patients with type 2 diabetes and patients with nephropathy and hypertension before modelling studies can be performed to project the long-term effects in this population.

With the exception of the German study, where life expectancy data were not published, the modelling studies reviewed confirmed that a reduction in progression to DSC and ESRD associated with irbesartan treatment led to an important improvement in life expectancy. A reduction in total lifetime costs of medications and ESRD per patient compared to treatment with amlodipine or the control was reported in all eight settings. Based on the published modelling studies, it appears that irbesartan has a valuable role to play in reducing the huge clinical and economic burden associated with ESRD in patients with type 2 diabetes, advanced overt nephropathy and hypertension.

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